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IBM Technical Disclosure Bulletins

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Search History

DATE: Thursday, May 13, 2004 Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=PGPB,USPT; PLUR=YES; OP=AND			
L3	l1 with L2	3	L3
L2	srage or soluble adj receptor near3 advanc$ adj glycation adj endproduct	34	L2
L1	(prevent$ or protect$) near8 (restenosis or atherosclerosis or diabetes)	9975	L1

END OF SEARCH HISTORY

h e b b g e e e e f ff e ch

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Search Results - Record(s) 1 through 3 of 3 returned.

☐ 1. 20030166063. 05 Mar 02. 04 Sep 03. High level insect expression of rage proteins. Harris, Robert B., et al. 435/69.1; 435/320.1 435/348 435/456 C12P021/02 C12N005/06 C12N015/86.

☐ 2. 20020122799. 01 Jun 01. 05 Sep 02. Methods for treating inflammation. Stern, David M., et al. 424/143.1; 514/12 514/23 514/44 A61K048/00 A61K038/17 A61K039/395 A61K031/70.

☑ 3. 20010039256. 05 Aug 97. 08 Nov 01. METHOD TO PREVENT ACCELERATED ATHEROSCLEROSIS USING (SRAGE) SOLUBLE RECEPTOR FOR ADVANCED GLYCATION ENDPRODUCTS. STERN, DAVID, et al. 514/2; 514/12 A01N037/18 A61K038/00.

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Terms	Documents
L1 with L2	3

Prev Page Next Page Go to Doc#

09/687,528

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=> d his

     (FILE 'HOME' ENTERED AT 16:07:01 ON 13 MAY 2004)

     FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 16:07:14 ON 13 MAY
     2004
L1            2 S SRAGE(6A)(DNA OR CDNA OR POLYNUCLEOTIDE OR NUCLEIC(W)ACID OR
L2          167 S SRAGE OR SOLUBLE(W)RAGE
L3           15 S L2(6A)(DNA OR CDNA OR POLYNUCLEOTIDE OR NUCLEIC(W)ACID OR PR
L4            2 DUP REM L1 (0 DUPLICATES REMOVED)
L5            8 DUP REM L3 (7 DUPLICATES REMOVED)
L6           90 DUP REM L2 (77 DUPLICATES REMOVED)
L7            9 S L2 AND REVIEW
L8            7 DUP REM L7 (2 DUPLICATES REMOVED)

=> d bib ab 1-7 l8

L8   ANSWER 1 OF 7  CAPLUS  COPYRIGHT 2004 ACS on STN
AN   2003:674927  CAPLUS
DN   139:289901
TI   The AGE-RAGE system and diabetic nephropathy
AU   Sakurai, Shigeru; Yonekura, Hideto; Yamamoto, Yasuhiko; Watanabe, Takuo;
     Tanaka, Nobushige; Li, Hui; Rahman, A. K. M. Azadur; Myint, Khin-Mar; Kim,
     Chul-Hee; Yamamoto, Hiroshi
CS   Department of Biochemistry and Molecular Vascular Biology, Kanazawa
     University Graduate School of Medical Science, Kanazawa, Japan
SO   Journal of the American Society of Nephrology (2003), 14(Suppl. 3),
     S259-S263
     CODEN: JASNEU; ISSN: 1046-6673
PB   Lippincott Williams & Wilkins
DT   Journal; General Review
LA   English
AB   A review. As is diabetes itself, diabetic vasculopathy is a
     multifactor disease. Studies revealed advanced glycation end products
     (AGE) as the major environmental account for vascular cell derangement
     characteristic of diabetes and the receptor for AGE (RAGE) as the major
     genic factor that responds to them. AGE fractions that caused the
     vascular derangement were proved to be RAGE ligands. When made diabetic,
     RAGE transgenic mice exhibited the exacerbation of the indexes of
     nephropathy and retinopathy, and this was prevented by the inhibition of
     AGE formation. Extracellular signals and nuclear factors that induce the
     transcription of human RAGE gene were also identified, which would be
     regarded as risk factors of diabetic complications. Through an anal. of
     vascular polysomal poly(A)+RNA, a novel splice variant coding for a
     sol. RAGE protein was found and was named endogenous
     secretory RAGE. Endogenous secretory RAGE was able to capture AGE ligands
     and to neutralize the AGE action on endothelial cells, suggesting that
     this variant has a potential to protect blood vessels from
     diabetes-induced injury. The AGE-RAGE system, therefore, should be a
     candidate mol. target for overcoming this life- and quality-of-life-
     threatening disease.
RE.CNT  21    THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8   ANSWER 2 OF 7  CAPLUS  COPYRIGHT 2004 ACS on STN
AN   2001:661126  CAPLUS
DN   136:83473
TI   Inflammation in nonhealing diabetic wounds: The space-time continuum does
     matter
AU   Pierce, Glenn F.
CS   Selective Genetics, San Diego, CA, 92121, USA
SO   American Journal of Pathology (2001), 159(2), 399-403
     CODEN: AJPAA4; ISSN: 0002-9440
PB   American Society for Investigative Pathology
```

DT Journal; General Review
LA English
AB A **review** describes the role of advanced glycation end products-receptor for AGE (RAGE) axis in nonhealing diabetic wounds. The biol. of nonhealing wounds and the roles of inflammation and proteases in tissue repair are also discussed. Studies showed that the well-recognized impaired wound healing in the db/db mouse, a model that approximates many of the features of type 2 diabetes in humans, could be ameliorated by administration of **sol. RAGE**.
RE.CNT 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 7 MEDLINE on STN DUPLICATE 1
AN 2002206063 MEDLINE
DN PubMed ID: 11938556
TI [Antioxidant and anti-AGE therapeutics: evaluation and perspectives]. Therapeutiques anti-oxydantes et anti-AGE: bilans et perspectives.
AU Bonnefont-Rousselot D
CS Laboratoire de Biochimie Metabolique et Clinique, UFR des Sciences Pharmaceutiques et Biologiques, 4, avenue de l'Observatoire, 75270 Paris, France.
SO Journal de la Societe de biologie, (2001) 195 (4) 391-8. Ref: 76
Journal code: 100890617.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA French
FS Priority Journals
EM 200204
ED Entered STN: 20020410
Last Updated on STN: 20020430
Entered Medline: 20020429
AB Diabetic patients exhibit an oxidative stress status, that is an imbalance between reactive oxygen species and antioxidant defences, in favour of the first ones. This oxidative stress, together with formation of advanced glycation endproducts (AGEs), is involved in diabetic complications. It could thus be of great interest to propose antioxidant and/or anti-AGE therapeutics as complementary treatment in these patients. Antioxidants can be classical molecules such as vitamin E, lipoic acid or N-acetylcysteine. Thus, vitamin E supplementation can improve insulin efficiency and glycemic equilibrium, as shown by the decrease of glycaemia, glycated haemoglobin and fructosamine values. In addition, this kind of supplementation lowers plasma lipid peroxidation and oxidizability of low density lipoproteins, which is involved in the atherogenesis process. Moreover, it allows to fight against complications such as retinopathy. A second category is represented by molecules able to fight against the effects of glycation end-products (AGEs). They can act: either by preventing cellular action of AGEs; this is obtained with soluble receptors of advanced glycation endproducts (**sRAGE**); or by inhibiting AGE formation (scavenging of reactive carbonyl intermediates). Nucleophilic compounds such as pyridoxamine, tenilsetam, 2,3-diaminophenazone, OPB-9195 or aminoguanidine can act in this way. Aminoguanidine is able to limit the development of the main diabetes-associated complications in animals. A double-blind clinical assay has been conducted in type 2 diabetic patients in the United States and the Canada, in order to determine if aminoguanidine is able to slow down the progression of diabetes-induced nephropathy. We will discuss about another guanidic molecule, i.e. metformin, which is also able to scavenge AGEs, in the last part of this **review**. A third category of molecules is constituted by oral antidiabetic molecules exhibiting antioxidant properties. They are thiazolidinediones (troglitazone) and sulfonylureas (gliclazide). Troglitazone and gliclazide can thus decrease LDL oxidizability and monocyte adhesion to

endothelial cells, which is an early step in the atherogenesis process and which is stimulated by oxidised LDLs. Finally, a prospective way is devoted to oral antidiabetic drugs exhibiting both antioxidant and anti-AGE properties. A very used antidiabetic drug of interest is metformin (dimethylbiguanide), since it can prevent diabetes complications not only by lowering glycaemia, but also by inhibiting AGE formation and by stimulating antioxidant defences. The latter therapeutic approach constitutes a future way in the diabetes area, in order both to obtain a better glycemic control and a least development of diabetic complications.

L8 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:776343 CAPLUS
DN 136:276788
TI Advanced glycation end products and the progressive course of renal disease
AU Heidland, August; Sebekova, Katarina; Schinzel, Reinhard
CS Department of Internal Medicine and Physiologische Chemie I, University of Wurzburg, Wurzburg, 97080, Germany
SO American Journal of Kidney Diseases (2001), 38(4, Suppl. 1), S100-S106
CODEN: AJKDDP; ISSN: 0272-6386
PB W. B. Saunders Co.
DT Journal; General Review
LA English
AB A **review**. In exptl. and human diabetic nephropathy (DN), it has been shown that advanced glycation end products (AGEs), in particular, carboxymethyl-lysine and pentosidine, accumulate with malondialdehyde in glomerular lesions in relation to disease severity and in the presence of an upregulated receptor for AGE (RAGE) in podocytes. Toxic effects of AGEs result from structural and functional alterations in plasma and extracellular matrix (ECM) proteins, in particular, from crosslinking of proteins and interaction of AGEs with their receptors and/or binding proteins. In mesangial and endothelial cells, the AGE-RAGE interaction caused enhanced formation of oxygen radicals with subsequent activation of nuclear factor-κB and release of pro-inflammatory cytokines (interleukin-6, tumor necrosis factor-α), growth factors (transforming growth factor-β1 [TGF-β1], insulin-like growth factor-1), and adhesion mols. (vascular cell adhesion mol.-1, intercellular adhesion mol.-1). In tubular cells, incubation with AGE albumin was followed by stimulation of the mitogen-activating protein (MAP) kinase pathway and its downstream target, the activating protein-1 (AP-1) complex, TGF-β1 overexpression, enhanced protein kinase C activity, decreased cell proliferation, and impaired protein degradation rate, in part caused by decreased cathepsin activities. The pathogenic relevance of AGEs was further verified by in vivo expts. in euglycemic rats and mice by the parenteral administration of AGE albumin, leading in the glomeruli to TGF-β1 overprodn., enhanced gene expression of ECM proteins, and morphol. lesions similar to those of DN. Evidence for the pathogenic relevance of AGEs in DN also comes from exptl. studies in which the formation and/or action of AGEs was modulated by aminoguanidine, OPB-9195, pyridoxamine, **sol. RAGEs**, serine protease trypsin, and antioxidants, resulting in improved cell and/or renal function.
RE.CNT 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:200797 CAPLUS
DN 131:3477
TI Activation of receptor for advanced glycation end products: a mechanism for chronic vascular dysfunction in diabetic vasculopathy and atherosclerosis
AU Schmidt, Ann Marie; Yan, Shi Du; Wautier, Jean-Luc; Stern, David
CS Division of Surgical Science, Departments of Surgery, College of Physicians and Surgeons of Columbia University, New York, NY, 10032, USA

SO Circulation Research (1999), 84(5), 489-497
CODEN: CIRUAL; ISSN: 0009-7330
PB Lippincott Williams & Wilkins
DT Journal; General Review
LA English
AB A **review** with 89 refs. Receptor for advanced glycation end products (RAGE) is a member of the Ig superfamily of cell surface mols. and engages diverse ligands relevant to distinct pathol. processes. One class of RAGE ligands includes glycoxidn. products, termed advanced glycation end products, which occur in diabetes, at sites of oxidant stress in tissues, and in renal failure and amyloidoses. RAGE also functions as a signal transduction receptor for amyloid β peptide, known to accumulate in Alzheimer disease in both affected brain parenchyma and cerebral vasculature. Interaction of RAGE with these ligands enhances receptor expression and initiates a pos. feedback loop whereby receptor occupancy triggers increased RAGE expression, thereby perpetuating another wave of cellular activation. Sustained expression of RAGE by critical target cells, including endothelium, smooth muscle cells, mononuclear phagocytes, and neurons, in proximity to these ligands, sets the stage for chronic cellular activation and tissue damage. In a model of accelerated atherosclerosis associated with diabetes in genetically manipulated mice, blockade of cell surface RAGE by infusion of a soluble, truncated form of the receptor completely suppressed enhanced formation of vascular lesions. Amelioration of atherosclerosis in these diabetic/atherosclerotic animals by **sol. RAGE** occurred in the absence of changes in plasma lipids or glycemia, emphasizing the contribution of a lipid- and glycemia-independent mechanism(s) to atherogenesis, which the authors postulate to be interaction of RAGE with its ligands. Future studies using mice in which RAGE expression has been genetically manipulated and with selective low mol. weight RAGE inhibitors will be required to definitively assign a critical role for RAGE activation in diabetic vasculopathy. However, sustained receptor expression in a microenvironment with a plethora of ligand makes possible prolonged receptor stimulation, suggesting that interaction of cellular RAGE with its ligands could be a factor contributing to a range of important chronic disorders.
RE.CNT 89 THERE ARE 89 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:154167 CAPLUS
DN 126:210315
TI The receptor for advanced glycation end-products has a central role in mediating the effects of advanced glycation end-products on the development of vascular disease in diabetes mellitus
AU Hori, Osamu; Yan, Shi Du; Ogawa, Satoshi; Kuwabara, Keisuke; Matsumoto, Masayasu; Stern, David; Schmidt, Ann Marie
CS Departments of Physiology, Medicine, Pathology and Surgery, Columbia University College of Physician and Surgeons, New York, NY, 10032, USA
SO Nephrology, Dialysis, Transplantation (1996), 11(Suppl. 5, Advanced Glycation End-Products in Diabetes Mellitus and Renal Failure), 13-16
CODEN: NDTREA; ISSN: 0931-0509
PB Oxford University Press
DT Journal; General Review
LA English
AB A **review** with 26 refs. Proteins or lipids exposed to aldose sugars undergo initial and ultimately irreversible modification resulting in the formation of so-called advanced glycation end-products (AGEs). AGEs are postulated to be especially important in the setting of diabetes mellitus due to hyperglycemia characteristic of this disorder. The work has demonstrated that one of the principal means by which AGEs interact with the vascular wall is by interaction with their cellular receptor, the receptor for advanced glycation end-products (RAGE), which is present on the surface of endothelial cells, smooth muscle cells, mesangial cells,

mononuclear phagocytes and certain neurons. AGEs interact with RAGE, resulting in the induction of monocyte chemotaxis as well as oxidant stress. One of the consequences of AGE-RAGE-induced cellular oxidant stress is the enhanced expression of vascular cell adhesion mol.-1 on the endothelial surface, a critical consequence of which is the attraction of mononuclear phagocytes into the vessel wall. In both cases, the pro-inflammatory effects of AGEs may be inhibited in the presence of RAGE blockade, using either anti-RAGE F(ab')2 or **sol. RAGE**, the extracellular domain of the mol. These data suggest that inhibition of RAGE may interfere with monocyte chemotaxis and attraction into the vessel wall where AGEs deposit/form, suggesting the potential of this intervention to interfere with a critical step in the development of vascular disease, especially in patients with diabetes.

L8 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:278136 CAPLUS
DN 122:52029
TI Cellular receptors for advanced glycation endproducts
AU Schmidt, A. M.; Stern, D. M.
CS Departments of Medicine and Physiology, Columbia University, College of Physicians and Surgeons, New York, NY, 10032, USA
SO Special Publication - Royal Society of Chemistry (1994), 151(Maillard Reactions in Chemistry, Food, and Health), 262-6
CODEN: SROCDO; ISSN: 0260-6291
DT Journal; General Review
LA English
AB A **review**, with .apprx.15 refs. Advanced glycation endproducts of proteins/lipids (AGEs) which form as the result of nonenzymic glycation/oxidation, are present in the plasma and tissues in aging, and accumulate more rapidly in diabetes. The interaction of AGEs with cellular elements, such as endothelial cells and mononuclear phagocytes leads to cellular dysfunction which could underlie the development of complications, such as accelerated atherosclerosis in diabetes. To gain insights into the cellular effects of AGEs, the authors have isolated and characterized 2 cell surface-associated polypeptides which appear to mediate the interaction with AGEs: receptor for AGE (RAGE) is a new member of the Ig superfamily of cell surface mols., and the lactoferrin-like polypeptide (LF-L) is closely related/identical to milk-derived lactoferrin. RAGE and LF-L associate to form a noncovalent complex on endothelial cells and mononuclear phagocytes which mediates the interaction of these cells with AGEs. For example, soluble AGE-bearing proteins induce monocyte migration, which can be blocked by antibody to either RAGE or LF-L, or by addition of **sol. RAGE**. Future studies using mol. probes for RAGE/LF-L should allow the definition of their contribution(s) to the development of organ dysfunction/complications in diabetes.

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(FILE 'HOME' ENTERED AT 16:07:01 ON 13 MAY 2004)

FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 16:07:14 ON 13 MAY 2004

L1 2 S SRAGE(6A)(DNA OR CDNA OR POLYNUCLEOTIDE OR NUCLEIC(W)ACID OR
L2 167 S SRAGE OR SOLUBLE(W)RAGE
L3 15 S L2(6A)(DNA OR CDNA OR POLYNUCLEOTIDE OR NUCLEIC(W)ACID OR PR
L4 2 DUP REM L1 (0 DUPLICATES REMOVED)
L5 8 DUP REM L3 (7 DUPLICATES REMOVED)

=> d bib ab 1-8 l5

L5 ANSWER 1 OF 8 MEDLINE on STN DUPLICATE 1
AN 2004140113 IN-PROCESS
DN PubMed ID: 15033494
TI S100 protein translocation in response to extracellular S100 is mediated by receptor for advanced glycation endproducts in human endothelial cells.
AU Hsieh Hsiao-Ling; Schafer Beat W; Weigle Bernd; Heizmann Claus W
CS Department of Pediatrics, Division of Clinical Chemistry and Biochemistry, University of Zurich, Steinwiesstr. 75, CH-8032 Zurich, Switzerland.
SO Biochemical and biophysical research communications, (2004 Apr 9) 316 (3) 949-59.
Journal code: 0372516. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20040323
Last Updated on STN: 20040410
AB The extracellular functions of S100 proteins have attracted more attention in recent years. S100 proteins are a group of calcium-binding proteins which exhibit cell- and tissue-specific expression, and different expression levels of members from this family have been observed in various pathological conditions. The reported extracellular functions of S100 proteins include the ability to enhance neurite outgrowth, involvement in inflammation, and motility of tumour cells. In our previous study, we reported translocation of S100A13 in response to the elevated intracellular calcium levels induced by angiotensin II. In order to investigate potential effects of extracellular S100A13, recombinant S100A13 was used here to stimulate human endothelial cells. Addition of extracellular S100A13 to the cells resulted in both endogenous protein translocation and protein uptake from the extracellular space. To test specificity of this effect, addition of various other S100 proteins was also performed. Interestingly, translocation of specific S100 proteins was only observed when the cells were stimulated with the same extracellular S100 protein. Since the receptor for advanced glycation end products (RAGE) is a putative cell surface receptor for S100 proteins and is involved in various signal transduction pathways, we next investigated the interaction between the receptor and extracellular S100 proteins. We show here that NF-kappaB which is a downstream regulator in RAGE-mediated transduction pathways can be activated by addition of extracellular S100 proteins, and translocation of S100 **proteins** was inhibited by **soluble RAGE**. These experiments suggest a common cell surface receptor for S100 proteins on endothelial cells even though intracellular translocation induced by extracellular S100 proteins is specific.

L5 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:644192 CAPLUS
DN 139:175557
TI RAGE peptide fragments as inhibitors of interaction of advanced glycation

endproducts (AGE) with its receptor (RAGE), and therapeutic applications
IN Yamamoto, Hiroshi; Yonekura, Hideto; Watanabe, Takuo; Yamamoto, Yasuhiko; Sakurai, Shigeru
PA Kanazawa University, Japan
SO Jpn. Kokai Tokkyo Koho, 23 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI JP 2003230382	A2	20030819	JP 2002-32155	20020208
PRAI JP 2002-32155		20020208		

AB Peptide inhibitors of the interaction of advanced glycation endproducts (AGE) with cell surface receptor for AGE (RAGE), and use in anal. or inhibition of AGE-RAGE interactions, are disclosed. Use of the peptide inhibitors as therapeutic agents for diabetes complications, aging associated diseases, Alzheimer's disease, arteriosclerosis, onset or progression of disease caused by protein glycation, tumor infiltration or diffusion, is claimed. Therapeutic agents for prevention or treatment of diabetes, diabetes complications, diabetic nephropathy, diabetic vascular diseases, diabetic capillary diseases, glomerular sclerosis, hyperlipidemic atherosclerosis, neuro toxicity, Down syndrome, head injury-associated dementia, amyotrophic lateral sclerosis, multiple sclerosis, amyloidosis, autoimmune disease, inflammation, tumor, cancer, erectile disfunction, wound healing, periodontal disease, neuropathy, and neurodegenerative disease, are also claimed. CDNA encoding the soluble form of RAGE was cloned from primary culture of human skin microvasculature endothelial cells and expressed in COS-7 cells. Oligopeptides corresponding to the N-terminal Ig-like domain were synthesized to study their effects on AGE-RAGE interactions. Oligopeptide V-N1 inhibited the interaction of RAGE with glyceraldehyde-derived AGE (AGE-2), and oligopeptide V-N2 inhibited the interaction of RAGE with glycolaldehyde--derived AGE (AGE-3).

L5 ANSWER 3 OF 8 MEDLINE on STN DUPLICATE 2
AN 2003342051 MEDLINE
DN PubMed ID: 12874443
TI The AGE-RAGE system and diabetic nephropathy.
AU Sakurai Shigeru; Yonekura Hideto; Yamamoto Yasuhiko; Watanabe Takuo; Tanaka Nobushige; Li Hui; Rahman A K M Azadur; Myint Khin-Mar; Kim Chul-Hee; Yamamoto Hiroshi
CS Department of Biochemistry and Molecular Vascular Biology, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan.
SO Journal of the American Society of Nephrology : JASN, (2003 Aug) 14 (8 Suppl 3) S259-63. Ref: 21
Journal code: 9013836. ISSN: 1046-6673.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200311
ED Entered STN: 20030723
Last Updated on STN: 20031113
Entered Medline: 20031112

AB As is diabetes itself, diabetic vasculopathy is a multifactor disease. Studies revealed advanced glycation end products (AGE) as the major environmental account for vascular cell derangement characteristic of diabetes and the receptor for AGE (RAGE) as the major genic factor that responds to them. AGE fractions that caused the vascular derangement were proved to be RAGE ligands. When made diabetic, RAGE transgenic mice exhibited the exacerbation of the indices of nephropathy and retinopathy, and this was prevented by the inhibition of AGE formation. Extracellular

signals and nuclear factors that induce the transcription of human RAGE gene were also identified, which would be regarded as risk factors of diabetic complications. Through an analysis of vascular polysomal poly(A)(+)RNA, a novel splice variant coding for a **soluble RAGE protein** was found and was named endogenous secretory RAGE. Endogenous secretory RAGE was able to capture AGE ligands and to neutralize the AGE action on endothelial cells, suggesting that this variant has a potential to protect blood vessels from diabetes-induced injury. The AGE-RAGE system, therefore, should be a candidate molecular target for overcoming this life- and quality-of-life-threatening disease.

L5 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 3
AN 2003:674927 CAPLUS
DN 139:289901
TI The AGE-RAGE system and diabetic nephropathy
AU Sakurai, Shigeru; Yonekura, Hideto; Yamamoto, Yasuhiko; Watanabe, Takuo; Tanaka, Nobushige; Li, Hui; Rahman, A. K. M. Azadur; Myint, Khin-Mar; Kim, Chul-Hee; Yamamoto, Hiroshi
CS Department of Biochemistry and Molecular Vascular Biology, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan
SO Journal of the American Society of Nephrology (2003), 14(Suppl. 3), S259-S263
CODEN: JASNEU; ISSN: 1046-6673
PB Lippincott Williams & Wilkins
DT Journal; General Review
LA English
AB A review. As is diabetes itself, diabetic vasculopathy is a multifactor disease. Studies revealed advanced glycation end products (AGE) as the major environmental account for vascular cell derangement characteristic of diabetes and the receptor for AGE (RAGE) as the major genic factor that responds to them. AGE fractions that caused the vascular derangement were proved to be RAGE ligands. When made diabetic, RAGE transgenic mice exhibited the exacerbation of the indexes of nephropathy and retinopathy, and this was prevented by the inhibition of AGE formation. Extracellular signals and nuclear factors that induce the transcription of human RAGE gene were also identified, which would be regarded as risk factors of diabetic complications. Through an anal. of vascular polysomal poly(A)+RNA, a novel splice variant coding for a **sol. RAGE protein** was found and was named endogenous secretory RAGE. Endogenous secretory RAGE was able to capture AGE ligands and to neutralize the AGE action on endothelial cells, suggesting that this variant has a potential to protect blood vessels from diabetes-induced injury. The AGE-RAGE system, therefore, should be a candidate mol. target for overcoming this life- and quality-of-life-threatening disease.
RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:718508 CAPLUS
DN 140:161549
TI Regulation of receptor for advanced glycation end products during bleomycin-induced lung injury
AU Hanford, Lana E.; Fattman, Cheryl L.; Schaefer, Lisa M.; Enghild, Jan J.; Valnickova, Zuzana; Oury, Tim D.
CS Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
SO American Journal of Respiratory Cell and Molecular Biology (2003), 29(3, Pt. 2), S77-S81
CODEN: AJRBEL; ISSN: 1044-1549
PB American Thoracic Society
DT Journal
LA English

AB The bleomycin model of pulmonary fibrosis was used to investigate the changes in the levels of soluble receptor for advanced glycation end products (sRAGE) and membrane-bound RAGE as pulmonary fibrosis progresses. Bleomycin injury leads to a significant loss of pulmonary **sRAGE**, a **protein** predicted to have beneficial protective effects against inflammatory injuries. The simultaneous loss of membrane RAGE in this injury model was also observed These findings suggest that alterations in RAGE signaling pathways may contribute to the pathogenesis of pulmonary fibrosis.
RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:130592 CAPLUS
DN 130:148702
TI Method to prevent accelerated atherosclerosis using soluble receptor for advanced glycation endproducts (sRAGE)
IN Stern, David; Schmidt, Ann Marie
PA The Trustees of Columbia University in the City of New York, USA
SO PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9907402	A1	19990218	WO 1998-US16303	19980805
	W: AU, CA, JP, MX, US				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 2001039256	A1	20011108	US 1997-905709	19970805
	AU 9888239	A1	19990301	AU 1998-88239	19980805
	AU 758252	B2	20030320		
	EP 1011706	A1	20000628	EP 1998-939876	19980805
	EP 1011706	B1	20031112		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2001513511	T2	20010904	JP 2000-506991	19980805
	AT 253929	E	20031115	AT 1998-939876	19980805
PRAI	US 1997-905709	A2	19970805		
	WO 1998-US16303	W	19980805		

AB A method is provided for prevention of accelerated atherosclerosis in a subject predisposed thereto which comprises administering to the subject a polypeptide derived from soluble receptor for advanced glycation endproduct in an amount effective to prevent accelerated atherosclerosis in the subject. Also provided is a method to prevent a macrovessel disease in a subject predisposed thereto which comprises administering to the subject a polypeptide derived from soluble receptor for advanced glycation endproduct in an amount effective to prevent macrovessel disease in the subject.
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:696864 CAPLUS
DN 128:10317
TI Advanced glycosylation end-product receptor peptides and their uses for increasing vascular permeability in disease conditions
IN Morser, Michael John; Nagashima, Mariko
PA Schering Aktiengesellschaft, Germany
SO PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9739121	A1	19971023	WO 1997-EP1832	19970411
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9726960	A1	19971107	AU 1997-26960	19970411
	ZA 9703242	A	19980805	ZA 1997-3242	19970416
PRAI	US 1996-633147		19960416		
	WO 1997-EP1832		19970411		

AB Compns. are provided that specifically interact with advanced glycosylation end-products (AGEs) or their receptors (RAGE). Thus, **DNA** coding for human **sol**. **RAGE** was obtained from a human lung **cDNA** library using PCR techniques. Human RAGE cDNA encodes a receptor precursor sequence of 350 amino acids comprising a 22-residue signal moiety and a 318-residue mature receptor. Solid phase binding assays for soluble human RAGE as well as competition binding assays using soluble human RAGE are described. Monoclonal antibodies specific for epitope peptides of soluble human RAGE are prepared and useful in various immunoassay techniques. Soluble RAGE is shown to increase vascular permeability by (a) in vitro permeability studies, (b) TBIR (tissue-blood-isotope ratio) studies, (c) albumin clearance studies in STZ-induced diabetic rats, and (d) single microvessel studies. Such compns. may be used in a variety of applications including therapeutic applications, e.g., as blocking agents to inhibit or otherwise reduce the AGE/RAGE interaction, screening applications, e.g., as models of the AGE/RAGE interaction, and diagnostic applications, e.g., to identify abnormal levels of AGE or RAGE in a given system.

L5 ANSWER 8 OF 8 MEDLINE on STN DUPLICATE 4
AN 97368045 MEDLINE
DN PubMed ID: 9224812
TI Recombinant advanced glycation end product receptor pharmacokinetics in normal and diabetic rats.
AU Renard C; Chappey O; Wautier M P; Nagashima M; Lundh E; Morser J; Zhao L; Schmidt A M; Scherrmann J M; Wautier J L
CS Laboratoire de Recherche en Biologie Vasculaire et Cellulaire, Universite Paris 7, Hopital Lariboisiere, France.
SO Molecular pharmacology, (1997 Jul) 52 (1) 54-62.
Journal code: 0035623. ISSN: 0026-895X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199708
ED Entered STN: 19970825
Last Updated on STN: 19970825
Entered Medline: 19970808
AB Vascular dysfunction in patients with diabetes mellitus is related to advanced glycation end product (AGE) formation. We previously showed that AGEs produce an increase in vascular permeability and generated an oxidant stress after binding to the receptor (RAGE) present on endothelium. RAGE, a 35-kDa protein that belongs to the immunoglobulin superfamily, has been cloned from a rat lung **cDNA** library, and recombinant rat **soluble RAGE** (rR-RAGE) has been produced in insect cells. The sequence of RAGE is highly conserved between human and rat. We studied the biological effect of rR-RAGE and pharmacokinetics of 125I-rR-RAGE after intravenous or intraperitoneal administration in normal and streptozotocin-induced diabetic rats. rR-RAGE prevented albumin or

inulin transfer through a bovine aortic endothelial cell monolayer, restored the hyperpermeability observed in diabetic rats or induced in normal rats by diabetic rat red blood cells, and corrected the reactive oxygen intermediate production after intravenous or intraperitoneal administration. After intravenous injection of 125I-rR-RAGE, the distribution half-life was longer ($p < or = 0.01$) in diabetic (0.15 and 4.01 hr) than in normal (0.02 and 0.21 hr) rats, as was the case for the elimination half-lives (diabetic, 57.17 hr; normal, 26.02 hr; $p < or = 0.01$). Distribution volume was higher in diabetic than in normal rats (6.94 and 3.24 liter/kg, respectively; $p = 0.049$). Our study showed that rR-RAGE was biologically active in vivo and slowly cleared, which suggests it could be considered as a potential therapy.

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09/687,528

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=> d his

     (FILE 'HOME' ENTERED AT 14:52:54 ON 13 MAY 2004)

     FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 14:53:12 ON 13 MAY
     2004
L1        31487 S (PREVENT? OR PROTECT?)(8A)(RESTENOSIS OR ATHEROSCLEROSIS OR D
L2           92 S SRAGE OR SOLUBLE(W)RECEPTOR(3A)ADVANC?(W)GLYCATION(W)ENDPRODU
L3            1 S L1(6A)L2
L4            6 S L1 AND L2
L5            4 DUP REM L4 (2 DUPLICATES REMOVED)

=> d bib ab 1-4 l5

L5   ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2004 ACS on STN
AN   2002:293614  CAPLUS
DN   136:304083
TI   A method for inhibiting new tissue growth in blood vessels in a patient
     subjected to blood vessel injury
IN   Stern, David M.; Schmidt, Ann-Marie; Marso, Steven; Topol, Eric; Lincoff,
     A. Michael
PA   The Trustees of Columbia University In the City of New York, USA
SO   PCT Int. Appl., 43 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
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PI   WO 2002030889      A2   20020418       WO 2001-US32036  20011012
     WO 2002030889      A3   20020711
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL,
             PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,
             UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
             BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     AU 2002013192      A5   20020422       AU 2002-13192    20011012
PRAI US 2000-687528     A    20001013
     WO 2001-US32036    W    20011012
AB   This invention provides for a method for inhibiting new tissue growth in
     blood vessels in a subject, wherein the subject experienced blood vessels
     injury, which comprises administering to the subject a pharmaceutically
     effective amount of an inhibitor of receptor for advanced glycation
     endproduct (RAGE) so as to inhibit new tissue growth in the subject's
     blood vessels. The invention also provides for method for inhibiting
     neointimal formation in blood vessels in a subject, wherein the subject
     experienced blood vessel injury, which comprises administering to the
     subject a pharmaceutically effective amount of an inhibitor of receptor for
     advanced glycation endproduct (RAGE) so as to inhibit neointimal formation
     in the subject's blood vessels. The invention also provides a method for
     preventing exaggerated restenosis in a diabetic subject
     which comprises administering to the subject a pharmaceutically effective
     amount of an inhibitor of receptor for advanced glycation endproduct (RAGE)
     so as to prevent exaggerated restenosis in the
     subject. In the example provided, a significant reduction in neointimal area
     was observed in fatty Zucker rats treated with sol.
     receptor for advanced glycation
     endproduct following carotid artery injury.

L5   ANSWER 2 OF 4      MEDLINE on STN                    DUPLICATE 1
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AN 2002206063 MEDLINE
DN PubMed ID: 11938556
TI [Antioxidant and anti-AGE therapeutics: evaluation and perspectives]. Therapeutiques anti-oxydantes et anti-AGE: bilans et perspectives.
AU Bonnefont-Rousselot D
CS Laboratoire de Biochimie Metabolique et Clinique, UFR des Sciences Pharmaceutiques et Biologiques, 4, avenue de l'Observatoire, 75270 Paris, France.
SO Journal de la Societe de biologie, (2001) 195 (4) 391-8. Ref: 76 Journal code: 100890617.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA French
FS Priority Journals
EM 200204
ED Entered STN: 20020410
Last Updated on STN: 20020430
Entered Medline: 20020429
AB Diabetic patients exhibit an oxidative stress status, that is an imbalance between reactive oxygen species and antioxidant defences, in favour of the first ones. This oxidative stress, together with formation of advanced glycation endproducts (AGEs), is involved in diabetic complications. It could thus be of great interest to propose antioxidant and/or anti-AGE therapeutics as complementary treatment in these patients. Antioxidants can be classical molecules such as vitamin E, lipoic acid or N-acetylcysteine. Thus, vitamin E supplementation can improve insulin efficiency and glycemic equilibrium, as shown by the decrease of glycaemia, glycated haemoglobin and fructosamine values. In addition, this kind of supplementation lowers plasma lipid peroxidation and oxidizability of low density lipoproteins, which is involved in the atherogenesis process. Moreover, it allows to fight against complications such as retinopathy. A second category is represented by molecules able to fight against the effects of glycation end-products (AGEs). They can act: either by preventing cellular action of AGEs; this is obtained with **soluble receptors** of **advanced glycation endproducts** (**sRAGE**); or by inhibiting AGE formation (scavenging of reactive carbonyl intermediates). Nucleophilic compounds such as pyridoxamine, tenilsetam, 2,3-diaminophenazone, OPB-9195 or aminoguanidine can act in this way. Aminoguanidine is able to limit the development of the main diabetes-associated complications in animals. A double-blind clinical assay has been conducted in type 2 diabetic patients in the United States and the Canada, in order to determine if aminoguanidine is able to slow down the progression of diabetes-induced nephropathy. We will discuss about another guanidic molecule, i.e. metformin, which is also able to scavenge AGEs, in the last part of this review. A third category of molecules is constituted by oral antidiabetic molecules exhibiting antioxidant properties. They are thiazolidinediones (troglitazone) and sulfonylureas (gliclazide). Troglitazone and gliclazide can thus decrease LDL oxidizability and monocyte adhesion to endothelial cells, which is an early step in the atherogenesis process and which is stimulated by oxidised LDLs. Finally, a prospective way is devoted to oral antidiabetic drugs exhibiting both antioxidant and anti-AGE properties. A very used antidiabetic drug of interest is metformin (dimethylbiguanide), since it can **prevent diabetes** complications not only by lowering glycaemia, but also by inhibiting AGE formation and by stimulating antioxidant defences. The latter therapeutic approach constitutes a future way in the diabetes area, in order both to obtain a better glycemic control and a least development of diabetic complications.

L5 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:130592 CAPLUS

DN 130:148702
TI Method to **prevent** accelerated **atherosclerosis** using **soluble receptor** for **advanced glycation endproducts (sRAGE)**
IN Stern, David; Schmidt, Ann Marie
PA The Trustees of Columbia University in the City of New York, USA
SO PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9907402	A1	19990218	WO 1998-US16303	19980805
	W: AU, CA, JP, MX, US				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 2001039256	A1	20011108	US 1997-905709	19970805
	AU 9888239	A1	19990301	AU 1998-88239	19980805
	AU 758252	B2	20030320		
	EP 1011706	A1	20000628	EP 1998-939876	19980805
	EP 1011706	B1	20031112		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2001513511	T2	20010904	JP 2000-506991	19980805
	AT 253929	E	20031115	AT 1998-939876	19980805
PRAI	US 1997-905709	A2	19970805		
	WO 1998-US16303	W	19980805		

AB A method is provided for **prevention** of accelerated **atherosclerosis** in a subject predisposed thereto which comprises administering to the subject a polypeptide derived from **sol. receptor** for **advanced glycation endproduct** in an amount effective to **prevent** accelerated **atherosclerosis** in the subject. Also provided is a method to prevent a macrovessel disease in a subject predisposed thereto which comprises administering to the subject a polypeptide derived from **sol. receptor** for **advanced glycation endproduct** in an amount effective to prevent macrovessel disease in the subject.
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:351788 CAPLUS
DN 129:12747
TI Method for treating symptoms of **diabetes** with agents **preventing** binding of advanced glycation endproducts to receptors
IN Stern, David M.; Schmidt, Ann Marie
PA Trustees of Columbia University in the City of New York, USA
SO PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9822138	A1	19980528	WO 1997-US21197	19971112
	W: AU, CA, JP, MX				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 2003059423	A1	20030327	US 1996-755235	19961122
	AU 9852639	A1	19980610	AU 1998-52639	19971112
	AU 745241	B2	20020314		
	EP 946196	A1	19991006	EP 1997-947592	19971112
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

IE, FI

JP 2001504493 T2 20010403 JP 1998-523860 19971112

PRAI US 1996-755235 A 19961122

WO 1997-US21197 W 19971112

AB A method is provided for treating symptoms of diabetes in a diabetic subject, e.g. abnormal wound healing, which comprises administering to the subject a therapeutically effective amount of an agent which inhibits binding of advanced glycation endproducts to any receptor for advanced glycation endproducts so as to treat chronic symptoms of diabetes in the subject. Improved wound healing in diabetic mice by treatment with the **sol. receptor** for **advanced glycation endproducts** is described.

RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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